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Effect of drug particle size in ultrasound compacted tablets Continuum percolation model approach

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Abstract

The main objective of this work is to study the influence of the drug particle size on the pharmaceutical availability of ultrasound compacted tablets. Inert matrix systems containing different drug particle sizes were prepared using both, an ultrasound-assisted press and a traditional eccentric machine. Potassium chloride was used as drug model and Eudragit® RS-PM as matrix forming excipient. The excipient particle size was kept constant. The cross-sectional microphotographs of ultrasound tablets show the existence of a quasi-continuum medium. Keeping constant the drug load, US-tablets showed very similar release rates, whereas for traditional tablets, an increase in the particle size resulted in a clear decrease in the release rate. In these tablets, the excipient forms an almost continuum medium. In an infinite theoretical system of these characteristics, the size of the drug particles will not modify the percolation threshold. The percolation of the excipient in this system can be assimilated to a continuum percolation model. In accordance with the proposed model, a lower influence of the drug particle size on the drug release rate was obtained for the US-tablets in comparison with traditional tablets. This fact can be indicative of the similarity of the drug percolation thresholds in these systems.
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Keywords: Matrix tablet; Ultrasound-assisted press; Continuum percolation; Percolation threshold

1. Introduction

The compression of a powder is a complex process that is usually affected by different kinds of problems. These problems have been widely investigated and mainly concern the volume reduction and the development of strength between the particles of the powder, sufficient to keep the tablet integrity (Leuenberger and Rohera, 1986). The application of ultrasonic energy is showing a great ability to reduce and even avoid these problems (Levina et al., 2000).

Ultrasound-assisted compression can provide a new tool to prepare Controlled Release Systems in a simple way. One of the reasons for this technique being not widely used in pharmaceutical technology can be the lack of a clear knowledge on the effect of the application of ultrasonic energy on the final properties of the dosage form.

In this respect, the percolation theory is being applied to obtain a theoretical model able to predict the behaviour of the obtained systems.

This statistical theory supposes the existence of a regular lattice underlying the system. As a function of their relative volume ratios one or both components constitute a "percolating cluster", formed by particles of the same component that "touch" each other from one side to the other sides of the tablet, generating a continuous phase through the matrix. One of the most important parameters of percolation theory is the percolation threshold, where there is a maximum probability of appearance of an infinite or percolating cluster of a substance. This concentration usually represents a critical point of the system (Stauffer and Aharony, 1991). Close to this point, important changes can be observed, such as change in the release mechanism of the active agent or modification of the tablet structure (monolith versus a desegregating device, etc.). Details for the estimation of this threshold have been widely described elsewhere (Bonny and Leuenberger, 1991, 1993; Caraballo et al., 1993). The optimum concentration ranges for both, a drug and an insoluble polymer, have been defined as a function of the percolation thresholds of drug and excipient (Bonny and Leuenberger, 1991, 1993) with the purpose to prepare inert matrices.

Furthermore, the influence of the formulation parameters such as the particle size on the percolation threshold has

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been studied in previous works for traditional inert matrices (Caraballo et al., 1993, 1996; Millán et al., 1998) where a linear relationship was found between the relative drug/excipient particle size and the drug percolation threshold.

Recent studies (Caraballo et al., 2000) have shown that in case of one component of the system undergoing thermoplastic deformation, the continuum percolation model can be used to predict the changes in the system with respect to a traditional pharmaceutical dosage form.

The continuum percolation model dispenses with the existence of a regular lattice underlying the system; therefore, the substance is not distributed into discrete lattice sites. This model deals with the volume ratio of each component and a continuum distribution function. The volume ratio is expressed as a space–occupation probability to describe the behaviour of the substance (Efros, 1994; Kuentz and Leuenberger, 1998).

This model can explain the important decrease in the critical point corresponding to the excipient percolation threshold, a critical point that governs the mechanical and release properties of the matrix.

Ultrasound compaction lowers the percolation threshold of the thermoplastic excipient, resulting in a drastic reduction (about 50%) for matrix forming excipient, as well as in a better control of the drug release. The structure of the excipient inside the US-tablets does not correspond to a particulate system but to an almost continuum medium: therefore, there is no an excipient particle size inside these matrices. Consequently, the percolation threshold of the active agent is higher than in traditional tablets. The insoluble excipient almost surrounds the active agent particles, slowing down the contact with the dissolution medium. These facts can involve important advantages for the pharmaceutical industry, such as the preparation of controlled release inert matrices containing high drug doses, with a very little increase in the weight of the system. The application of the ultrasonic energy results in an increase in the temperature of the die during the compaction process. The consequences of this fact should be taken into account and cannot be neglected in the case of thermolabile drugs and/or excipients (Rodriguez et al., 1997, 1998).

The main objective of this study is to evaluate, for the first time, the effects of drug particle size on the pharmaceutical availability properties of ultrasound compacted tablets and to study the behaviour of a substance (a drug in this case) distributed as discrete particles into a continuum phase (the excipient) that surrounds the drug almost completely, applying the continuum percolation model.

2. Experimental

2.1. Materials

Potassium chloride (Acofarma, Barcelona) was used as water-soluble drug model and Eudragit® RS-PM (Hüls Española, Barcelona), a hydrophobic, non-swelling acrylic polymer, was used as matrix-forming material.

2.2. Methods

2.2.1. Preparation of tablets

Potassium chloride and Eudragit® RS-PM were sieved (Retsch type Vibro). The mean diameter of the particles of drug and excipient was measured using He–Ne laser diffraction system (Malvern Instr., type Mastersizer x, 1.2b). Table 1 shows the composition of the 50 formulations prepared, as well as the mean drug particle size employed. The excipient particle size (124 μm) was kept constant.

2.2.2. Compression process

Different lots were prepared using an ultrasound-assisted press and a traditional eccentric machine.

The traditional tablets were prepared by direct compression, using an eccentric machine (Bonals type A-300) at the maximum compression force accepted by the formulations, using a three-chamber compression matrix (12 mm diameter).

The US-tablets were prepared with a lab scale ultrasound-assisted tableting machine (Saitec Srl). This machine is equipped with an US generator coupled to the upper punch. An ultrasonic energy of 80 J was applied to the mixture during the compaction process at the frequency of 20 kHz. Flat cylindrical punches of 11 mm were employed.

Tablets with a weight of approximately 600 mg were obtained in both, US and traditional machines using manual feeding.

2.2.3. Technological parameters of the tablets

Weight (Mettler, mod. AE-50), height and diameter (Export-Pel micrometer) were determined as the mean of at least 10 tablets.

The initial porosity (ε_0) was determined based on the values of volume and weight:

$$\varepsilon_0 = \frac{V_{\text{real}} - V_{\text{theor}}}{V_{\text{real}}} \quad (1)$$

where V_{real} is the volume of the tablet and V_{theor} the theoretical volume of the tablet, corresponding to the sum of the volumes

Table 1
Composition, drug particle size and type of tabletting machine employed for the preparation of the studied formulations

Traditional eccentric % KCl	Particle size KCl (μm)[a]	Ultrasound-assisted % KCl
10, 20, 30, 40, 50, 60, 65, 70, 75, 80, 90	144	50
40, 50, 55, 60, 65, 70, 75, 80	210	10, 20, 30, 40, 50, 60, 70, 75, 80, 85, 90
40, 50, 55, 60, 65, 70, 75, 80	270	50
40, 50, 55, 60, 65, 70, 75, 80, 85	302	50

[a] The excipient particle size (124 μm) was kept constant.

obtained dividing the mass of each component by their true density.

The total porosity (ε) was obtained in a similar way:

$$\varepsilon = \frac{V_{real} - V_{exc}}{V_{real}} \quad (2)$$

V_{exc} the volume corresponding to the insoluble components of the system, i.e. the inert excipient and ε is the porosity of the matrix after dissolution of the soluble components of the tablet have been dissolved.

2.2.4. Dissolution profiles

Dissolution studies were carried out in the USP 28 apparatus (Turu Grau, type D-6) using the rotating disc method, so that only one surface of the tablet (0.79 cm^2 for US-tablets and 1.13 cm^2 for traditional tablets) was exposed to the dissolution medium (deaerated water at $37 \pm 0.5\,^{\circ}C$). The rotational speed was kept constant at 50 rpm. Release of KCl was detected by the increase in conductance of the dissolution medium, using a Crison micro CM-2201 digital conductivity-meter linked to a chart recorder and a personal computer. The system provided one conductivity datum per second. This analytical method has been validated in previous studies (Caraballo et al., 1998). Conductivity data were converted into percentage of KCl dissolved, by means of a calibration curve.

Higuchi's kinetic model (Higuchi, 1963) ($Q = a + bt^{1/2}$) was used to study the changes in the matrix release rate.

Experimental data were plotted as a function of the square root of the time (Higuchi plot). Only values in the range 10–70% of the total concentration were used for the linear regression in traditional tablets. The slope of the cumulative fractional release versus the square root of the time is called the Higuchi's slope throughout the paper. In case of US-tablets, based on the considerations exposed in Section 3.2, only values obtained after 150 min from the beginning of the release assay were used.

2.2.5. Estimation of the drug percolation threshold

To determine the percolation threshold, we have followed the method developed by Bonny and Leuenberger (1991). Therefore, the drug percolation threshold has been estimated plotting the β property versus the total porosity of the tablets. This property, derived from the diffusion coefficient, is defined by the following equation:

$$\beta = \frac{b}{\sqrt{2A - \varepsilon C_s}} \quad (3)$$

where b is the Higuchi's slope (g cm^{-2} $min^{-1/2}$), A the concentration of the dispersed drug in the tablet (g cm^{-3}) and C_s is the solubility of the drug in the permeating fluid (g cm^{-3}).

The parameter β linearly depends on the distance from the percolation threshold ε_c. Above the drug percolation threshold there is a range where the β property behaves as:

$$\beta = c(\varepsilon - \varepsilon_c) = -c\varepsilon_c - c\varepsilon \quad (4)$$

where c is a constant, ε the total porosity of the matrix due to initial tablet porosity and to drug content after leaching and ε_c denotes the drug percolation threshold expressed as critical porosity.

The values of the β property and the total porosity, ε, have been calculated individually for each one of the three replicates. The linear regression of β versus ε (concerning only the linear region of the plot above p_c) allows to estimate the drug percolation threshold.

2.2.6. Scanning electron microscopy (SEM)

A scanning electron microscope (Phillips type XL-30) with a back scattering electrons detector (BSE) and a secondary electrons (SE) detector was employed in order to study the surface and the cross-section of the matrix tablets.

3. Results and discussion

3.1. Scanning electron microscopy

In order to check whether the compression method has affected the drug particle size, the surface and the cross-section of the matrices were studied by SEM. No substantial modification of the drug particle size has been found in the surface of both tablets (Figs. 1 and 2).

The main difference observed studying the surfaces of traditional and US-tablets is the partial erosion of the edges of the KCl particles in tablets with higher drug particle size (see Figs. 1 and 2).

On the other hand, the cross-sectional microphotographs of tablets prepared using the ultrasound-assisted press, show the existence of a quasi-continuum medium, due to the important thermoplastic deformation (perhaps accompanied by partial fusion) of the excipient, by effect of the application of ultrasounds (Fig. 3). The cross-section of traditional tablet is shown in Fig. 4 for comparison purposes.

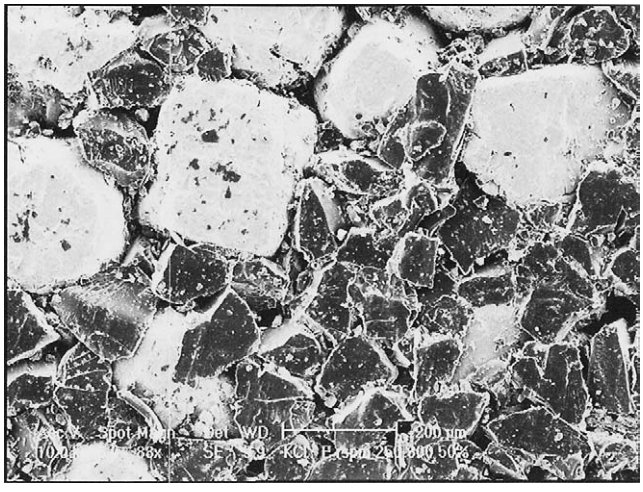

Fig. 1. SEM micrograph showing the surface of the US-tablets with 50% (w/w) drug content, using the SE detector.

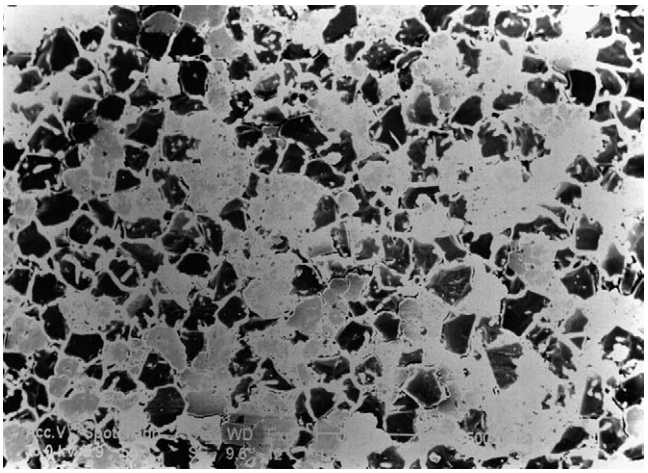

Fig. 2. SEM micrograph showing the surface of the traditional tablets with 50% (w/w) drug content, using the SE detector.

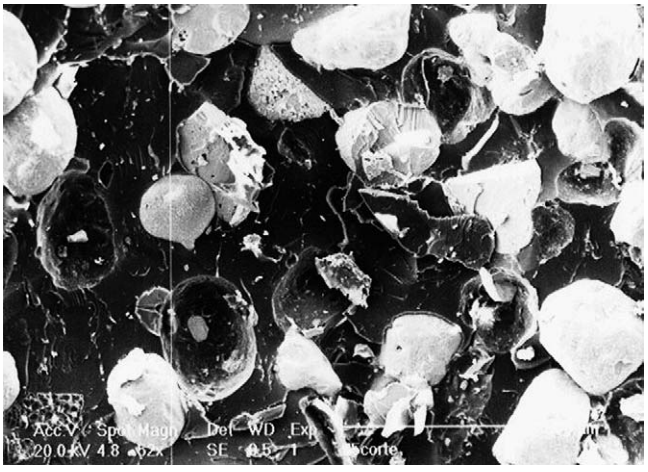

Fig. 3. SEM micrograph showing the cross-section of the US-tablets with 50% (w/w) drug content, using the SE detector. KCl (white particles) is surrounded by excipient (shadow).

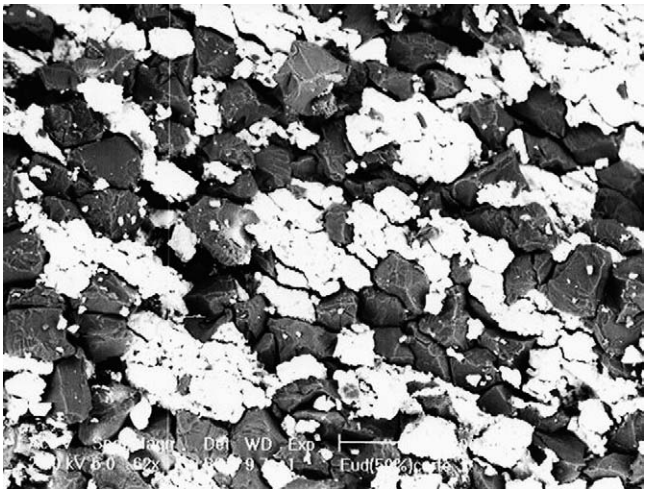

Fig. 4. SEM micrograph showing the cross-section of the traditional tablet with 50% (w/w) drug content, using the BSE detector. White particles correspond to KCl and shadow particles to the excipient.

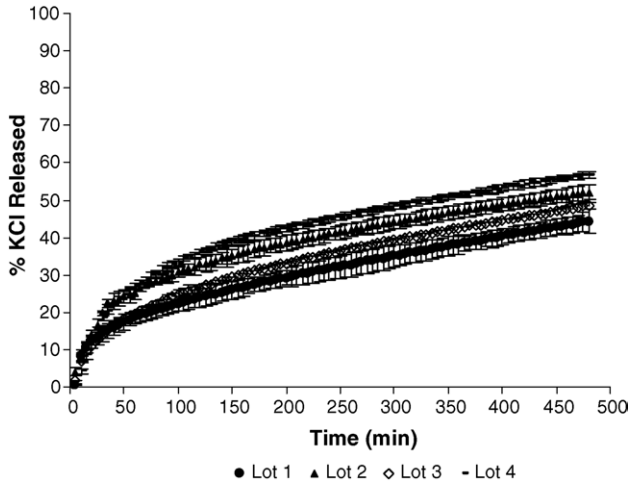

Fig. 5. Percent release profiles (mean of three replicates) of US-tablets containing 50% (w/w) KCl and 50% (w/w) excipient (mean values ± S.D., $n = 3$). (●) 144 μm; (▲) 210 μm; (◊) 270 μm; (–) 302 μm drug particle size and the excipient particle size (124 μm) was kept constant.

3.2. Release profiles and released kinetics

The obtained tablets were subjected to the dissolution test, following the conditions indicated in the previous section. Figs. 5 and 6 show the release profiles for both, traditional and US-tablets containing 50% (w/w) KCl and 50% (w/w) excipient.

A clear difference between the releases profiles of the US-tablets cannot be appreciated (Fig. 5). The opposite behaviour was obtained for the traditional tablets, where an increase in the particle size resulted in a clear decrease in the release rate (see Fig. 6).

Despite Fig. 5 shows some differences in the amount released; a detailed analysis of the release profiles of US-tablets indicates that, after the first stage, the release rate of the different lots are practically identical. This fact has been verified, calculating the Higuchi constant (Higuchi, 1963) of these lots for time >150 min. The results obtained confirm the proposed hypothesis (see Table 2). As it can be observed, very similar profiles were obtained showing no tendency against the particle size.

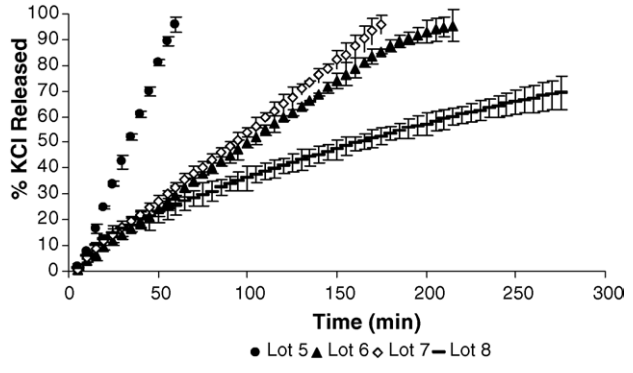

Fig. 6. Percent release profiles (mean of three replicates) of traditional tablets containing 50% (w/w) KCl and 50% (w/w) excipient (mean values ± S.D., $n = 3$). (●) 144 μm; (%) 210 μm; (◊) 270 μm; (–) 302 μm drug particle size and the excipient particle size (124 μm) was kept constant.

Table 2
Parameters corresponding to the calculation of the Higuchi's slope[a] of tablet containing 50% (w/w) KCl and 50% (w/w) excipient varying the drug particle size

Tabletting machine[b]	Particle size KCl (μm)[c]	*b*	*r*	*n*	*F*	Prob.
1	144	0.0297	0.999	81	45191.9305	<0.0001
1	210	0.0305	0.999	81	186633.03	<0.0001
1	270	0.0316	0.999	81	248972.87	<0.0001
1	302	0.0296	0.999	81	98400.047	<0.0001
2	144	0.0550	0.990	7	244.2	<0.0001
2	210	0.0279	0.986	27	905.9	<0.0001
2	270	0.0286	0.984	25	708.2	<0.0001
2	302	0.0170	0.998	43	9680.8	<0.0001

The tablets were prepared using both an ultrasound-assisted tabletting machine and a traditional eccentric machine.
[a] b = Higuchi constant ($g\,min^{-1/2}\,cm^{-2}$); r = linear correlation coefficient; n = number of cases; F = Snedecor ratio.
[b] 1, Ultrasound-assisted tabletting machine; 2, traditional eccentric tabletting machine.
[c] The excipient particle size (124 μm) was kept constant.

Table 3
Calculation of the tablet property β and related parameter[a] in matrices containing 50% (w/w) of drug, 124 μm Eudragit® RS-PM, varying the KCl particle size

Tabletting machine[b]	Particle size KCl (μm)	ε_0	ε	*b*	*r*	*n*	*F*	Prob.	*A*	$\beta \times 10^{-3}$
1	144	0.062	0.421	0.0297	0.999	81	45191.931	<0.0001	0.715	26.29
1	210	0.060	0.416	0.0305	0.999	81	186633.03	<0.0001	0.721	26.87
1	270	0.052	0.424	0.0316	0.999	81	248972.87	<0.0001	0.711	28.04
1	302	0.065	0.426	0.0296	0.999	81	98400.047	<0.0001	0.709	26.36
2	144	0.177	0.493	0.0550	0.990	7	244.2	<0.0001	0.626	57.82
2	210	0.150	0.477	0.0279	0.986	27	905.9	<0.0001	0.646	26.32
2	270	0.118	0.457	0.0286	0.984	25	708.2	<0.0001	0.670	28.66
2	302	0.138	0.469	0.0170	0.998	43	9680.8	<0.0001	0.656	15.93

The initial porosity (ε_0) of the tablets has been included. The tablets were prepared using both an ultrasound-assisted press and a traditional eccentric machine.
[a] ε, Total porosity; b, Higuchi constant ($g\,min^{-1/2}\,cm^{-2}$); r, linear correlation coefficient; n, number of cases; F, Snedecor ratio; A, concentration of drug dispersed in the tablet ($g\,cm^{-3}$); β, tablet property ($g^{1/2}\,cm^{-1/2}\,min^{-1/2}$).
[b] 1, Ultrasound-assisted; 2, traditional eccentric.

The differences observed in the first stage (0–150 min) can be attributed to the distortion introduced by the finite clusters of drug connected with the surface exposed to the dissolution medium (see Fig. 1). These clusters will form pores of higher size (in which the diffusion of the drug will be faster) when coarser drug particles are employed.

These results differ significantly from those obtained for tablets prepared with traditional machine, which show important differences in the release rate as a function of the particle size of drug (see Fig. 6 and Table 2).

3.3. Estimation of the drug percolation threshold

The drug percolation thresholds (p_{c1}) were calculated using the property β, proposed by Bonny and Leuenberger (1991), as described in Section 2. Table 3 shows the values of the parameters involved in the calculation of β for the matrix containing 50% (w/w) of drug and prepared using the traditional eccentric machine and ultrasound-assisted press, respectively.

In our study, the considered β values were those included in the following ranges of (w/w) KCl concentration: 40–80, 40–80, 40–80, 50–85%, respectively, for tables containing 144, 210, 270 and 302 μm KCl particles and prepared with a traditional eccentric machine. In the case of tablets prepared using, the ultrasound-assisted press the ranges of (w/w) KCl concentration were 75–90% for tablets containing 144 μm KCl.

Table 4 shows the drug percolation thresholds obtained as well as some statistical parameters from the determination the β values of both ultrasound and traditional tablets.

Table 4
Drug percolation thresholds (ε_c) and statistical parameters from their determination

Tabletting machine[a]	KCl particle size (μm)[b]	ε_c	*r*	*n*	*F*	Prob.
1	144	0.615	0.999	4	577.9008	<0.0001
2	144	0.345	0.863	7	14.6380	<0.0001
2	210	0.362	0.979	8	139.431	<0.0001
2	270	0.381	0.992	8	355.316	<0.0001
2	302	0.417	0.990	8	307.862	<0.0001

The tablets were prepared using two types of tabletting machines.
[a] 1, Ultrasound-assisted tabletting machines; 2, traditional eccentric tabletting machines.
[b] The excipient particle size (124 μm) was kept constant.

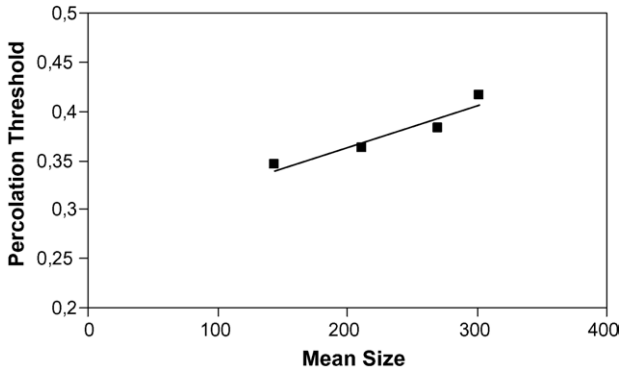

Fig. 7. Drug percolation thresholds obtained in traditional tablets as a function of the drug particle size (μm) employed.

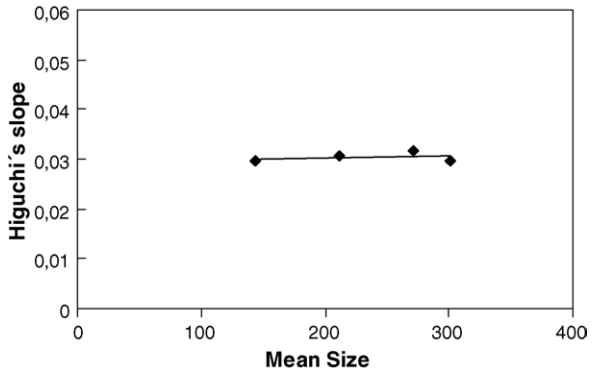

Fig. 9. Higuchi's slope ($g\,min^{-1/2}\,cm^{-2}$) of US-tablets containing 50% (w/w) of drug as a function of the mean particle size (μm) of the drug employed.

Fig. 7 shows the drug percolation thresholds obtained as a function of the drug particle size for lots with 124 μm diameter excipient in tablets prepared with the traditional eccentric machine.

As shown in this figure, linear changes in the drug percolation threshold were obtained by changing the drug particle size (Caraballo et al., 1996; Millán et al., 1998).

There is a clear influence of the drug particle size on the drug percolation threshold, which increases when coarser drug particles are employed.

As shown in Table 4, there is a remarkable difference between the percolation thresholds calculated for the 210 μm particle size fraction of KCl in traditional tablets and in US-tablets, showing the ultrasound-assisted tablets higher drug percolation threshold ($\varepsilon_c = 0.615$). This behaviour can be explained using the continuum percolation model (Efros, 1994; Caraballo et al., 2000).

3.4. Influence of drug particle size

In Figs. 8 and 9 can be seen the completely different kinetic behaviour that exhibit US-tablets compared to traditional tablets of similar composition. As the particle size of the drug increases, there is a lower control of the drug release. However, in the case of US-tablets the control of the release is similar for every particle size.

When studying the behaviour of a release parameter (Higuchi's slope) we can appreciate that in the case of traditional tablets, there is direct relation between the Higuchi's slope and the drug particle size (Fig. 8).

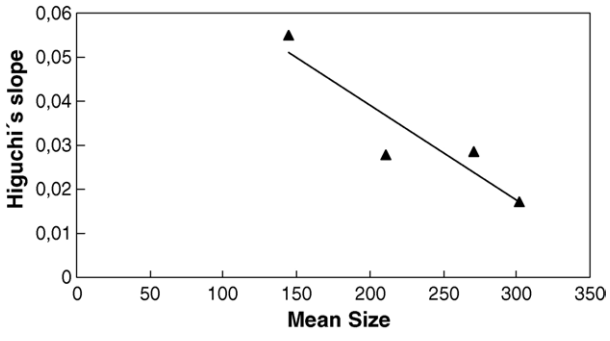

Fig. 8. Higuchi's slope ($g\,min^{-1/2}\,cm^{-2}$) of traditional tablets containing 50% (w/w) of drug as a function of the mean particle size (μm) of the drug employed.

This evolution of the Higuchi's slope, found in the traditional matrices studied, is inversely proportional to that found for the percolation threshold calculated for these matrices (Fig. 7).

However, in the case of US-tablets the release profiles are very similar, showing similar Higuchi's slope for the different particles sizes used (Fig. 9). This could indicate that the percolation thresholds of these tablets are very similar, being the similar distance to the percolation threshold the cause of the similarity in the release rates.

3.4.1. Effect of the sample size: influence in the percolation threshold

In the US-tablets there is no really a relative drug/excipient particle size, since the excipient forms an almost continuum medium. The percolation of the excipient in this system can be assimilated to a continuum percolation model. In this model, an underlying network does not exist and the components do not have a determined particle size. They behave like a fluid that crosses the system by random ways whose widths are changing within the same system.

This theoretical model is very similar for all the studied US-tablets: the drug particles are surrounded by the excipient, with the exception of the contact points between drug particles. In an infinite theoretical system of these characteristics, the size of the drug particles will not modify the percolation threshold.

Coming to our finite samples, the only difference between the lots would be the magnification with which the system is observed. Therefore, the lots with larger drug particles will correspond to the system observed with higher magnification and the lots with smaller drug particles could be represented by the same theoretical system, observed with a lower magnification.

The difference in the size of the particles implies that tablets prepared with 100–150 μm drug particles, contain a higher number of drug particles than the prepared with KCl of 150–200 μm. Therefore, the lot prepared with the fraction 250–300 μm, will contain the lower number of drug particles.

It can be expected that the average drug percolation threshold, measured in these lots, will only change by effect of the sample size, L (Stauffer and Aharony, 1991). This variation is described

by the following equation:

$$p_{c\,ave} - p_c \propto L^{-1/\nu}$$

being $p_{c\,ave}$ the average value of the percolation thresholds measured experimentally in the studied tablets, p_c the percolation threshold in the infinite theoretical system and ν a critical exponent, which in three-dimensions equals 0.9 (Deutscher et al., 1983).

Another factor that could influence in the obtained percolation thresholds would be the higher variability that can be expected in the lots with a minor number of drug particles. Nevertheless, this factor should not modify the average value of the percolation threshold, but its variability.

These two factors depending on the sample size are expected to have a little influence on the percolation threshold, compared to the inherent variability of the method for the estimation of the percolation threshold in our real systems. Therefore, this model predicts a low influence of the drug particle size on the drug release rate.

4. Conclusion

On the basis of the continuum percolation model, the US-tablets that contain a quasi-continuum mass of excipient, due to the effect of the ultrasonic energy on the thermoplastic acrylic excipient (Eudragit® RS-PM), constitute similar systems, independently of the drug particle size employed. Therefore, a lower influence of the particle size on the release properties was obtained for the US-tablets in comparison with traditional tablets. On the other hand, a lower variability in the pharmaceutical availability is expected for the systems obtained using ultrasound-assisted compression.

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